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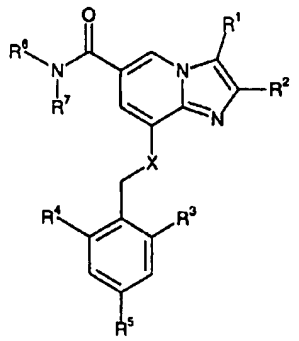

(I)

(57) Abstract

The present invention relates to imidazo pyridine derivatives of formula (I), in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with carboxamide group in 6-position, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases.

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IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

TECHNICAL FIELD

The present invention relates to novel compounds, and pharmaceutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above. The invention also relates to new intermediates for in the preparation of the novel compounds.

BACKGROUND ART

Substituted imidazo[1,2-a]pyridines, useful in the treatment of peptic ulcer diseases, are known in the art, e.g. from EP-B-0033094 and US 4,450,164 (Schering Corporation); from EP-B-0204285 and US 4,725,601 (Fujisawa Pharmaceutical Co.); and from publications by J. J. Kaminski et al. in the Journal of Medical Chemistry (vol. 28, 876-892, 1985; vol. 30, 2031-2046, 1987; vol. 30, 2047-2051, 1987; vol. 32, 1686-1700, 1989; and vol. 34, 533-541, 1991).

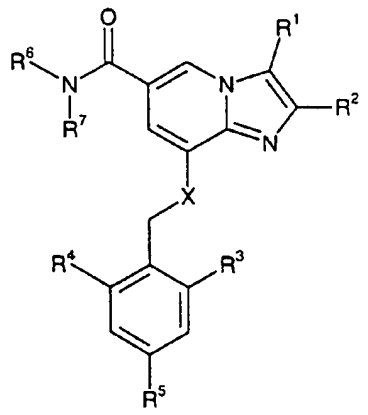
For a review of the pharmacology of the gastric acid pump (the H^+, K^+-ATPase), see Sachs et al. (1995) Annu. Rev. Pharmacol. Toxicol. 35: 277-305.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the Formula I, which are imidazo pyridine derivatives in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with a carboxamide group in 6-position are particularly

effective as inhibitors of the gastrointestinal H^+, K^+-ATPase and thereby as inhibitors of gastric acid secretion. The carboxamide group in 6-position is optionally selected to give compounds of Formula I a molecular weight ≤ 600.

In one aspect, the invention thus relates to compounds of the general Formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

(a) H,

(b) CH_3, or

(c) CH_2OH;

R^2 is

(a) CH_3, or

(b) CH_2CH_3;

R^3 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^4 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^5 is

(a) H, or

(b) halogen;

R^6 and R^7 are independently selected substituents, comprising C, H, N, O, S , Se , P and Halogen atoms, which give compounds of Formula I a molecular weight ≤ 600, provided that at least one of R^6 and R^7 can not be H, C_1–C_6 alkyl, hydroxylated C_1–C_6 alkyl,or C_1–C_6 alkoxy-substituted C_1–C_6 alkyl, and

X is

(a) NH, or

(b) O.

As used herein, the term "C_1–C_6 alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C_1–C_6 alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

The term "halogen" includes fluoro, chloro, bromo and iodo.

The substitutents R^6 and R^7 are defined as independently selected substituents, comprising C, H, N, O, S , Se , P or Halogen atoms, which give compounds of Formula I a molecular weight ≤ 600, which is a definition easily understood by a person skilled in the art.

Examples of substituents that fall within the scope of this definition includes, but is not limited to,

(a) H,

(b) C_1–C_6 alkyl,

(c) hydroxylated C_1–C_6 alkyl,

(d) C_1–C_6 alkoxy-substituted C_1–C_6 alkyl,

(e) C_2–C_6 alkenyl,

(f) C_2–C_6 alkynyl,

(g) halogenated C_1–C_6 alkyl,

(h) C_3–C_8 cycloalkyl,

(i) cycloalkyl-substituted C_1–C_6 alkyl,

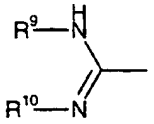
(j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, or CN or NH_2SO_2,

(k) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl , optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN or NH_2SO_2,

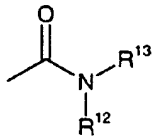
(l) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, NH_2SO_2–, C_1–C_6 alkyl–SO_2NH–, $ArSO_2NH$–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–SO_2–, C_1–C_6 alkyl–C=O–, NH_2–, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$N–, ArCONH–, Ar(C_1-C_6 alkyl)CONH, $ArNHSO_2$–, (Ar)$_2$–N–SO_2–, C_1–C_6 alkyl–$NHSO_2$–, ArS–, ArSO–, $ArSO_2$– ArC=O– NH_2CONH– C_1–C_6 alkyl-NHCONH– (C_1–C_6 alkyl)

(m) C_7-C_{12} ,

(n) OH, O-C_1–C_6 alkyl, or O-hydroxylated C_1–C_6 alkyl,

o)  wherein R^9 and R^{10} are independently H or C_1-C_6 alkyl,

p) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, C_1-C_6 alkyl-OOC- or an amino carbonyl group with the formula



wherein R^{12}, R^{13} are the same or different H, or C_1-C_6 alkyl

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline);

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention. It should be understood that all the diastereomeric forms possible (pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of the Formula I, such as prodrugs.

It will also be appreciated by those skilled in the art, although derivatives of compounds of formula I may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described

as "prodrugs". All prodrugs of compounds of formula I are included within the scope of the invention.

Depending on the process conditions the end products of the Formula I are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

In the preparation of acid addition salts, preferably such acids are used which form suitably pharmaceutically acceptable salts. Examples of such acids are hydrohalogen acids such as hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulphonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybensoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halogenbensenesulphonic acid, toluenesulphonic acid or naphthalenesulphonic acid.

Preferred compounds according to the invention are those of the Formula I wherein R^1 is CH_3 or CH_2OH; R^2 is CH_3 or CH_2CH_3; R^3 is CH_3 or CH_2CH_3; R^4 is CH_3 or CH_2CH_3; R^5 is H, Br, Cl, or F; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl or C_1-C_6 alkoxy-substituted C_1-C_6 alkyl):

(a) H,

(b) C_1–C_6 alkyl,

(c) hydroxylated C_1–C_6 alkyl,

(d) C_1–C_6 alkoxy-substituted C_1–C_6 alkyl,

(e) C_2–C_6 alkenyl,

(f) C_2–C_6 alkynyl,

(g) halogenated C_1–C_6 alkyl,

(h) C_3–C_8 cycloalkyl,

(i) cycloalkyl-substituted C_1–C_6 alkyl,

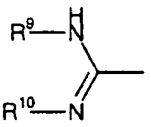
(j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, or CN or NH_2SO_2,

(k) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl , optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN or NH_2SO_2,

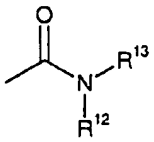
(l) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, NH_2SO_2–, C_1–C_6 alkyl–SO_2NH–, $ArSO_2NH$–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–SO_2–, C_1–C_6 alkyl–C=O–, NH_2–, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$N–, ArCONH–, Ar(C_1-C_6 alkyl)CONH, $ArNHSO_2$–, (Ar)$_2$–N–SO_2–, C_1–C_6 alkyl–$NHSO_2$–, ArS–, ArSO–, $ArSO_2$–, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl)$_2$–NCONH–, ArNHCONH–, (C_1–C_6 alkyl)$_2$–N–SO_2– , Ar–O– , Ar–NH– , Ar(C_1–C_6 alkyl)N– , (C_1–C_6 alkyl)$_2NSO_2$– , hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN, nitro, amino, C_1–C_6 alkyl–NH–, or (C_1–C_6 alkyl)$_2$N–,

(m) C_7-C_{12} ,

(n) OH, O-C_1–C_6 alkyl, or O-hydroxylated C_1–C_6 alkyl,

(o)  wherein R^9 and R^{10} are independently H or C_1-C_6 alkyl,

(p) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, C_1-C_6 alkyl-OOC- or an amino carbonyl group with the formula



wherein R^{12}, R^{13} are the same or different H, or C_1-C_6 alkyl

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, $(C_1$–C_6 alkyl$)_2$–N–, CN ,NH_2SO_2, phenyl. NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline);

More preferred compounds according to the invention are those of the Formula I wherein R^1 is CH_3 or CH_2OH; R^2 is CH_3, R^3 is CH_3 or CH_2CH_3; R^4 is CH_3 or CH_2CH_3; R^5 is H, Br, Cl, or F; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl or C_1-C_6 alkoxy-substituted C_1-C_6 alkyl)

:

(a) H,

(b) C_1–C_6 alkyl,

(c) hydroxylated C_1–C_6 alkyl,

(d) C_1–C_6 alkoxy-substituted C_1–C_6 alkyl,

(e) halogenated C_1–C_6 alkyl,

(f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, C_1–C_6 alkyl–NH–, $(C_1$–C_6 alkyl$)_2$–N–, or CN;

(g) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, or OH,

(h) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–C=O–,-ArCONH–, Ar(C_1-C_6 alkyl)CONH, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl)$_2$–NCONH–, ArNHCONH–,hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN,

(i) C_7-C_{12} alkyl.

(j) OH ,

(k) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, or C_1-C_6 alkyl-OOC

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline)

Most preferred compounds according to the invention are:

- 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine
- N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- N-[2-(dimethylamine)-2-oxoethyl]-8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide
- (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone
- 1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin -6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide
- 8-(2-ethyl-6-methylbenzylamino)-N-hydroxy-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

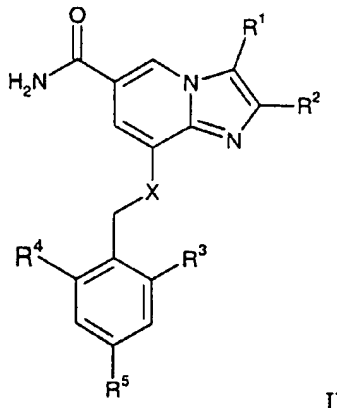
- (2-ethyl-6 methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-hydroxy-1-pyrrolidinyl)methanone
- N-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- 8-(2-ethyl-6-methylbenzylamino-3-(hydroxymethyl)-2-methyl-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine
- N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine
- 4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid

Preparation

The present invention also provides the following process for the manufacture of compounds with the general Formula I.

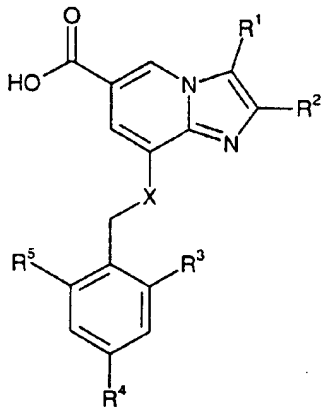
A process for manufacture of compounds with the general Formula I comprises the following steps:

a) Compounds of Formula II



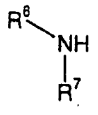
II

wherein R^1, R^2, R^3, R^4, R^5, and X are as defined in Formula I , can be hydrolyzed under standard conditions to the corresponding carboxylic acid to the corresponding carboxylic acid compounds of Formula III



III

b) Compounds of the Formula III wherein R^1, R^2, R^3, R^4, R^5 and X is as defined in Formula I can be reacted with amino compounds of Formula IV



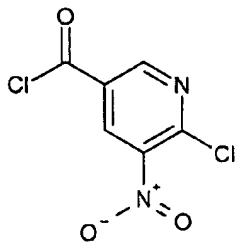
IV

wherein R^6 and R^7 are as defined for Formula I, in the presence of a coupling reagent to the corresponding amide compounds of the Formula I. The reaction can be carried out in an inert solvent under standard conditions.

The present invention also provides the following process for the manufacture of intermediate compounds with the general Formula II.

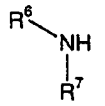
A process for manufacture of compounds with the general Formula II wherein X is NH comprises the following steps:

a) Compounds of the general Formula V



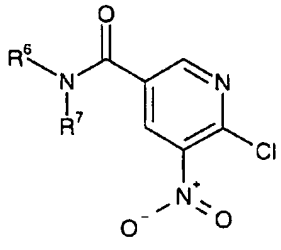
V

can be reacted with amino compounds of the general Formula IV



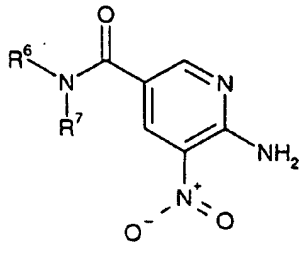
IV

wherein R^6 and R^7 are both hydrogen, to the corresponding amide of the Formula VI. The reaction can be carried out in standard conditions in an inert solvent.



VI

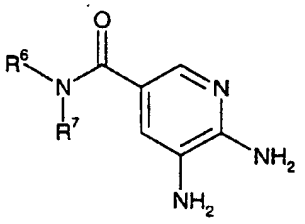
b) Compounds of the general Formula VI can be reacted with ammonia to compounds of the general Formula VII



VII

wherein R^6 and R^7 are both hydrogen. The reactions can be carried out under standard conditions in an inert solvent.

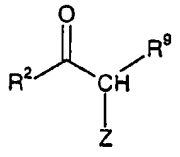
c) Compounds of the Formula VII can be reduced e.g. by using hydrogen and a catalyst such as Pd/C to compounds of the Formula VIII



VIII

wherein R^6 and R^7 are both hydrogen. The reaction can be carried out under standard conditions in an inert solvent.

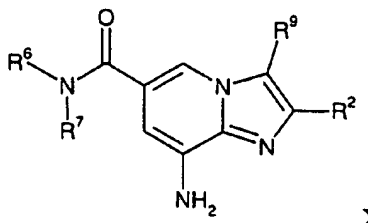
d) The imidazo[1,2-a]pyridine compounds of the Formula X can be prepared by reacting compounds of the general Formula VIII with compounds of the general Formula IX



IX

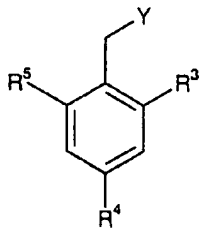
wherein R^2 is as defined for Formula I and Z is a leaving group such as halogen, mesyl, tosyl and R^9 represents H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$ etc.

The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, dimethylformamide, etc. with or without a base.



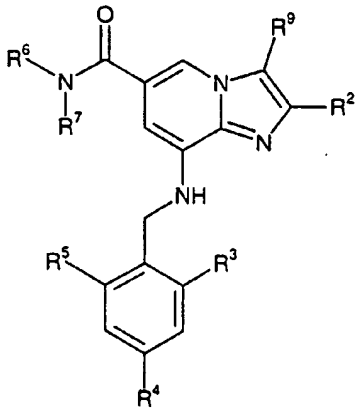
X

e) Compounds of the Formula X can be reacted with compounds of the Formula XI



XI

wherein R^3, R^4 and R^5 are as defined for Formula I and Y is a leaving group, such as a halide, tosyl or mesyl , to the compounds of the Formula XII.



XII

wherein R^2, R^3, R^4, and R^5 are as defined for Formula I and R^6 and R^7 both hydrogen and R_9 is H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc. It is convenient to conduct this reaction in an inert solvent, e.g. acetone, acetonitrile, dimethoxyethane, methanol, ethanol or dimethylformamide with or without a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide, an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine.

f) Reduction of compounds of the general Formula XII wherein R^9 is an ester group *e.g.* by using lithium borohydride in an inert solvent, such as tetrahydrofuran or diethyl ether, to the compounds of the general Formula I wherein R^1 is CH_2OH and R6 and R7 are both hydrogen.

Medical use

In a further aspect, the invention relates to compounds of the formula I for use in therapy, in particular for use against gastrointestinal inflammatory diseases. The invention also provides the use of a compound of the formula I in the manufacture of a medicament for the inhibition of gastric acid secretion, or for the treatment of gastrointestinal inflammatory diseases.

The compounds according to the invention may thus be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre-and postoperatively to prevent acid aspiration and stress ulceration.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance.

Pharmaceutical formulations

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof. as active ingredient.

The compounds of the invention can also be used in formulations together with other active ingredients, e.g. antibiotics such as amoxicillin.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains at least one compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1–95% by weight of the preparation, preferably between 0.1–20% by weight in preparations for parenteral use and preferably between 0.1 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Hard gelatin capsules may contain granules of the active compound. Hard gelatin capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatin rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.1% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to by reconstituted with a suitable solvent extemporaneously before use.

The compounds according to the present invention can also be used in formulations, together or in combination for simultaneous, separate or sequential use, with other active ingredients, *e.g.* for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa. Such other active ingredients may be antimicrobial agents, in particular:

- β-lactam antibiotics such as amoxicillin, ampicillin, cephalothin, cefaclor or cefixime;
- macrolides such as erythromycin, or clarithromycin;
- tetracyclines such as tetracycline or doxycycline;
- aminoglycosides such as gentamycin, kanamycin or amikacin;
- quinolones such as norfloxacin, ciprofloxacin or enoxacin;
- others such as metronidazole, nitrofurantoin or chloramphenicol; or
- preparations containing bismuth salts such as bismuth subcitrate, bismuth subsalicylate, bismuth subcarbonate, bismuth subnitrate or bismuth subgallate.

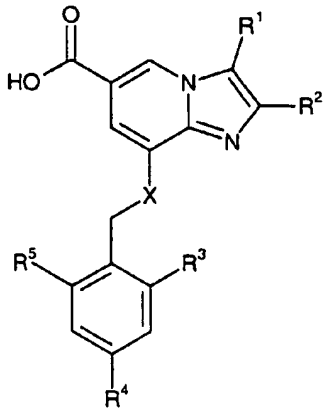
The compounds according to the present invention can also be used together or in combination for simultaneous, separate or sequential use with antacids such as aluminium hydroxide, magnesium carbonate and magnesium hydroxid or alginic acid, or together or in combination for simultaneous, separate or sequential use with pharmaceuticals which inhibit acid secretion, such as, H2-blockers (*e.g* cimetidine, ranitidine), H^+/K^+ - ATPase inhibitors (*e.g.* omeprazole, pantoprazole, lansoprazole or rabeprazole), or together or in combination for simultaneous, separate or sequential use with gastroprokinetics (*e.g.* cisapride or mosapride).

Intermediates

A further aspect of the invention is new intermediate compounds which are useful in the synthesis of compounds according to the invention.

Thus, the invention includes

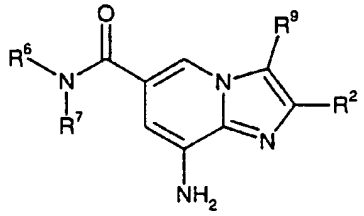
(a) a compound of the formula XVIII



XVIII

wherein R^1, R^2, R^3, R^4, R^5 and X are as defined for Formula I.

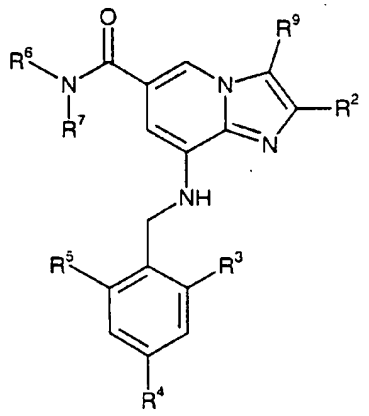
(b) a compound of the formula VIII



VIII

wherein R^2, R^6 and R^7 are as defined for Formula I, and R^9 is H, CH^3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc.;

(c) a compound of the formula X



X

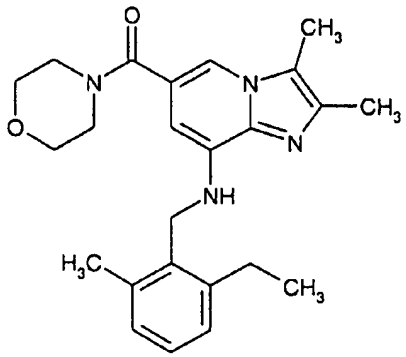
wherein R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for Formula I, and R^9 is an ester group such as $COOCH_3$, $COOC_2H_5$ etc.;

EXAMPLES

1. PREPARATION OF COMPOUNDS OF THE INVENTION

Example 1.1

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine

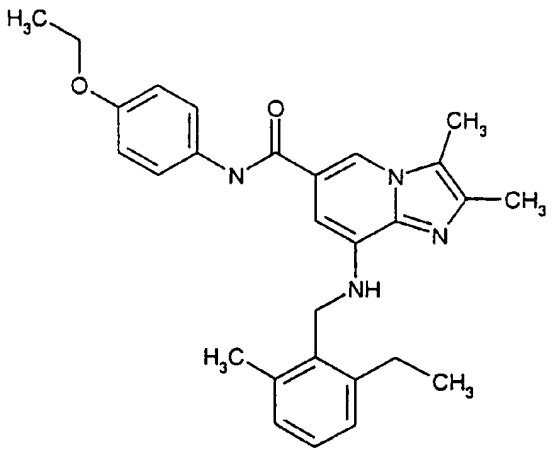


2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) were added to methylene chloride (10 ml). Morpholine (0.12 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was added to a column with silica gel and purification by chromatography using ethylacetate : methylene chloride (1:1) as eluent gave 0.12 g (66%) of the desired product.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 2.7 (q, 2H), 3.7 (s, 8H), 4.35 (d, 2H), 4.95 (bs, 1H), 6.15 (s, 1H), 7.0-7.2 (m, 3H), 7.4 (s, 1H)

Example 1.2

Synthesis of N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide



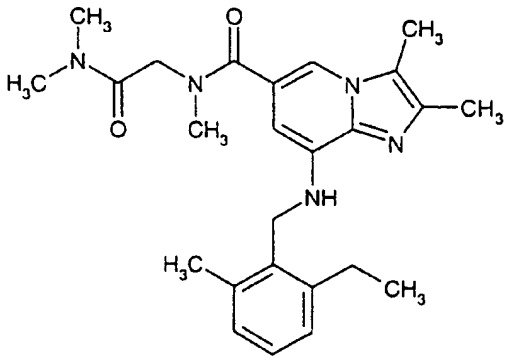
2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) were added to methylene chloride (10 ml). 4-ethoxyanilin(0.19 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 72 h. The solvent was evaporated under reduced pressure and the residue was added to a column with silica gel and was purified by chromatography using methylene chloride : methanol (95:5) as eluent. The residue was treated with a hot mixture

of hexane : ethyl acetate (2:1) and the product was filtered off and dried to obtain 0.14 g (74 %) of the desired compound as white crystals.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 1.4 (t,3H), 2.35 (s, 9H), 2.65 (q, 2H), 4.0 (q, 2H), 4.35 (d, 2H), 4.9 (t, 1H), 6.55 (s, 1H), 6.85 (d, 2H), 7.0-7.2 (m, 3H), 7.5 (d, 2H), 7.9 (s, 1H), 8.15 (s, 1H)

Example 1.3

Synthesis of N-[2-(dimethylamine)-2-oxoethyl]-8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide

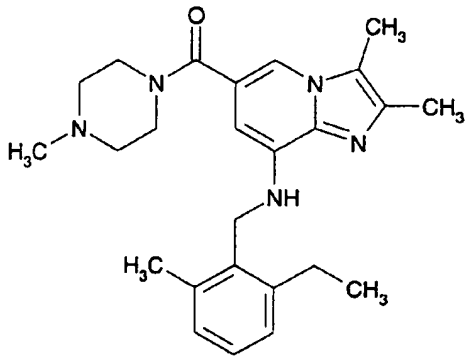


2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.13 g, 0.38 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU) (0.12 g, 0.38 mmol) were added to methylene chloride (10 ml). N,N.Dimethyl-2-methylamino-acetamide (0.088 g, 0.38 mmol) was added and the reaction mixture was stirred at ambient temperature for 1 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using methylene chloride : methanol as eluent (95:5) which gave 80 mg (48 %) of the title product.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.3 (s, 6H), 2.35 (s, 3H), 2.65 (q, 2H), 2.75 (s, 6H), 2.95 (s, 3H), 3.15 (s, 2H), 4.35 (bs, 2H), 4.85 (bs, 1H), 6.25 (s, 1H), 7.0-7.2 (m, 3H), 7.45 (s, 1H).

Example 1.4

Synthesis of (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone

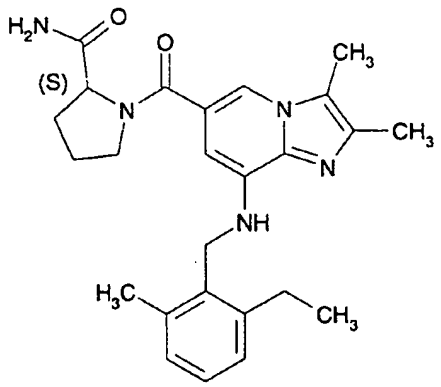


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.5 g, 1.48 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.48 g, 0.1.5 mmol) were added to methylene chloride (20 ml) and the mixture was stirred for 5 min. N-methylpiperazine (0.16g, 1.6 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent gave 0.46 g (74 %) of the title compound.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.22 (t, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.47 (bs, 4H), 2.71 (q, 2H), 2.80 (s, 3H), 3.65 (bs, 4H), 4.36 (d, 2H), 4.94 (t, 1H), 6.19 (s, 1H), 7.04-7.18 (m, 3H), 7.42 (s, 1H)

Example 1.5

Synthesis of 1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin -6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide

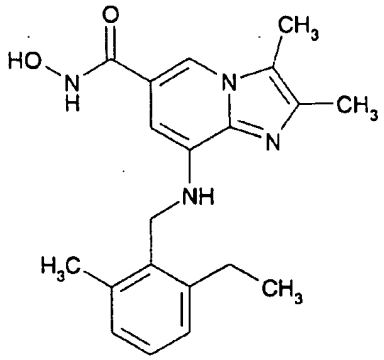


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.45 mmol) and triethylamine (0.05 g, 0.5 mmol) were added to methylene chloride (10 ml) and the mixture was stirred for 10 min.(S)-prolinamide (0.016 g, 0.45 mmol) was added and the reaction mixture was stirred at ambient temperature for 1 h.. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent and crystallization from diethyl ether gave 0.07 g (36 %) of the title compound.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.21 (t, 3H), 2.1-2.2 (m, 4H), 2.33 (s, 3H), 2.35 (s ,3H), 2.37 (s, 3H), 2.70 (q, 2H), 3.65-3.75 (m, 2H), 4.36 (d, 2H), 4.80 (bs, 1H), 4.94 (bs (1H), 5.88 (s, 1H), 6.33 (s, 1H), 6.98 (s, 1H), 7.04-7.19 (m,3H), 7.54 (s, 1H)

Example 1.6

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N-hydroxy-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide



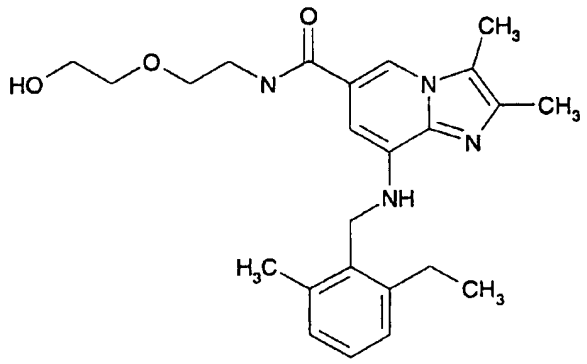
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.45 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.45 mmol), triethylamine (0.1 g, 0.99 mmol) and hydroxylamine hydrochloride (0.031 g, 0.46 mmol) in dimethylformamide (5 ml).

The title compound were prepared according to Example 1.5 (Yield: 0.016 g, 10 %)

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.15 (bs, 3H), 2,25 (bs, 9H), 2.6 (bs, 2H), 4.25 (bs, 2H), 4.95 (bs, 1H), 6.45 (bs, 1H), 6.9-7.1 (m, 3H), 7.75 (bs, 1H)

Example 1.7

Synthesis of (2-ethyl-6 methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide



2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate

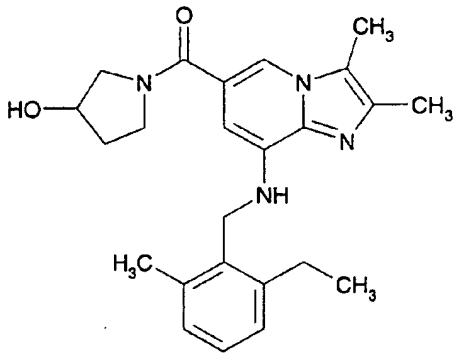
(TBTU)(0.29 g, 0.90 mmol) and 2-(2-aminoethoxy)ethanol (0.2 g, 1.9 mmol) in methylene chloride (10 ml).

The title compound were prepared according to Example 1.5 (Yield: 0.24 g, 80 %)

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.25 (t, 3H), 2.25 (s, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.75 (q, 2H), 3.4-3.45 (m, 2H), 3.55-3.7 (m, 6H), 4.35 (d, 2H), 5.05 (t, 1H), 6.45 (s, 1H), 7.0-7.2 (m, 4H), 7.5 (s, 1H)

Example 1.8

Synthesis of (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-hydroxy-1-pyrrolidinyl)methanone



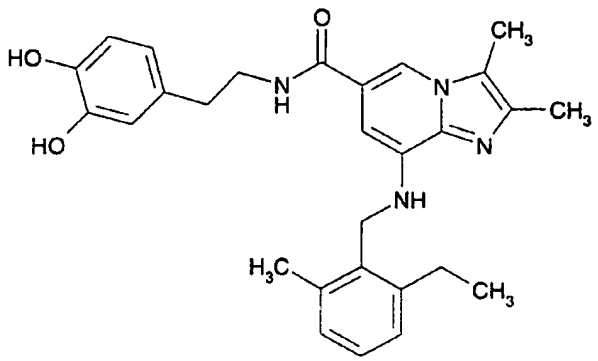
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) and 3-pyrrolidinol (0.12 g, 1.4 mmol) in methylene chloride (10 ml).

The title compound were prepared according to Example 1.4. Crystallization from ethylacetate:hexane (2:1) (Yield: 0.24 g, 80 %)

^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.23 (t, 3H), 1.93 (bs, 2H), 2.33 (s, 3H), 2.34 (s,3H), 2.41 (s, 3H), 2.70 (q, 2H), 3.51-3.89 (m, 4H), 4.35 (d, 2H), 4.38-4.55 (m, 1H), 5.04 (bs, 1H), 6.35 (s, 1H), 7.01-7.16 (m, 3H), 7.51 (s, 1H)

Example 1.9

Synthesis of N-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

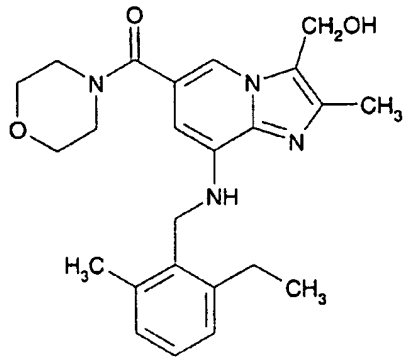


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.45 mmol) were added to dimethylformamide(10 ml) and the mixture was stirred for 5 min. 3,4-dihydroxyphenetylamin (0.27 g 1.4 mmol) and triethylamine (0.28 g, 1.4 mmol) were added was added and the reaction mixture was stirred at ambient temperature for 72 h.. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent and crystallization from acetonitrile gave 0.059 g (28 %) of the title compound.

^{1}H-NMR (400 MHz,DMSO-d_6): δ 1.15 (t, 1H), 2.22 (s, 3H), 2.33 (s, 3H), 2.37 (s, 3H), 2.65-2.74 (m, 4H), 3.41 (q, 2H), 4.37 (d, 2H), 4.85 (t, 1H), 6.48 (dd, 1H), 6.63-6.66 (m, 2H), 6.70 (d, 1H), 7.07-7.21 (m, 3H), 8.04 (d, 1H), 8.49 (t, 1H), 8.63 (s, 1H), 8.75 (s, 1H)

Example 1.10

Synthesis of 8-(2-ethyl-6-methylbenzylamino-3-(hydroxymethyl)-2-methyl-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine



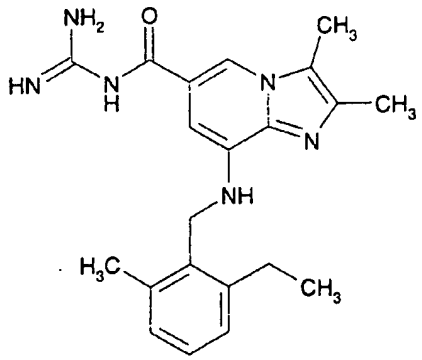
8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxylic acid (0.012 g, 0.034 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.011 g, 0.034 mmol) and morpholine (0.009 g, 0.1 mmol) in methylene chloride (1 ml)

The title compound were prepared according to Example 1.1. (Yield: 0.008 g, 56 %)

^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.23 (t, 3H), 2.33 (s, 3H), 2.39 (s, 3H), 2.72 (q, 2H), 3.74 (bs, 8H), 4.37 (d, 2H), 4.85 (s, 2H), 5.02 (t, 1H), 6.27 (d, 1H), 7.06-7.22 (m, 3H), 7.75 (d, 1H)

Example 1.86

Synthesis of N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine

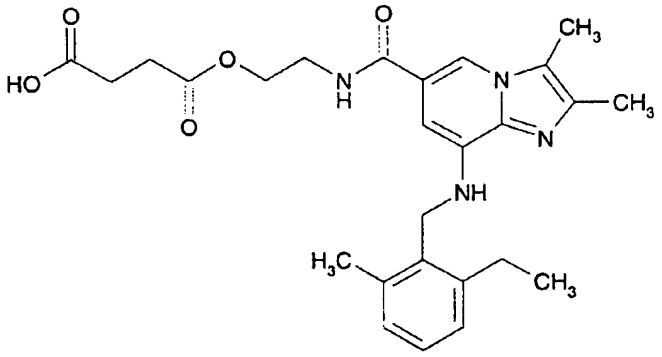


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.5 g, 1.5 mmol) , diisopropyethylamin (0.57 g, 1.5 mmol) and guanidine carbonate (0.53 g, 2.9 mmol) were added to dimethylformamide (10 ml). o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.48 g, 1.5 mmol) was added and the reaction mixture was stirred at 50 °C for 3 h.. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (100:15) as eluent and crystallization from diethyl ether gave 0.12 g (21 %) of the title compound.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.1 (t, 3H), 2.25 (s, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.35 (d, 2H), 4.8 (bs, 1H), 6.9 (s, 1H), 7.05-7.2 (m, 3H), 8.25 (s, 1H)

Example 1.87

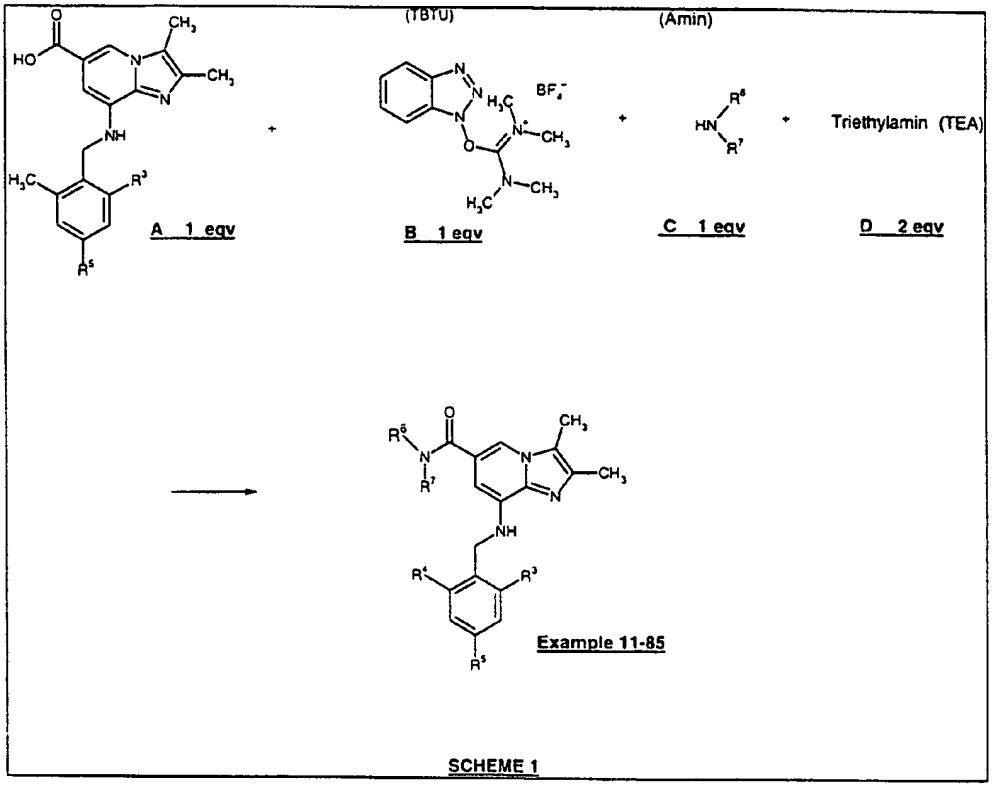
Synthesis of 4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid .



2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide (250 mg, 0.263 mmol) and succinic anhydride (100 mg, 1.00 mmol) were added to 7 ml of acetone. The mixture was refluxed for 48 h. The presiptated product was filtered off and washed with acetone and ether to give 288 mg (91%) of the title compound.

^{1}H-NMR (500 MHz, DMSO): δ 1.16 (t, 3H), 2.24 (s, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 2.48-2.58 (m, 4H), 2.70 (q, 2H), 3.54 (q, 2H), 4.19 (t, 2H), 4.39 (d, 2H), 4.90 (t, 1H), 6.72 (s, 1H), 7.09-7.22 (m, 3H), 8.08 (s, 1H), 8.59 (t, 1H), 12.25 (s, 1H).

Example 11-85 was prepared by parallell-synthesis using the following method:



SCHEME 1

Solution A : 0.149 mmol in 1 ml dimethylformamide

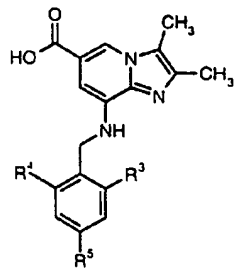
Solution B (TBTU): 0.297 mmol in 1 ml dimethylformamide

Solution C + D: Amin (C) (0.297 mmol in 1 ml dimethylformamide) + TEA (D) (0.594 mmol in 1 ml dimethylamin)

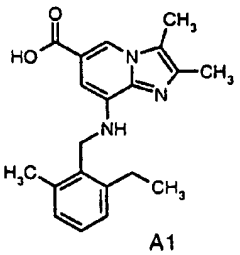
To a solution A (300 µl) were added solution B (150 µl) and solution C+D (150 µl). The reaction was stirred by shaking at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was solved in dichloromethane/methanol (9/1)(600 µl) and was filtred through a plug of silca gel (100 mg) and the gel was washed with dichloromethane/methanol (9/1) (0.5-1.0 ml). The filtrate was evaporated under reduced pressure to give the desired compounds. (If needed the compounds were purified by preparative HPLC.)

The analyses of the examples was made by HPLC and the compounds were identified by LC-mass spectroscopy. All compounds prepared in Example 11-85 showed a mass spectrum that confirmed the proposed structure.

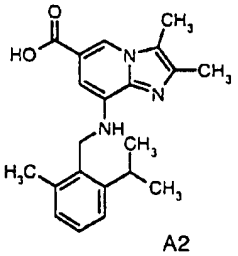
As the starting compound A in the reactions the following compounds were used.



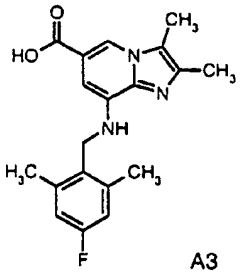
A =



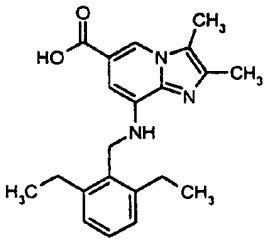
A1



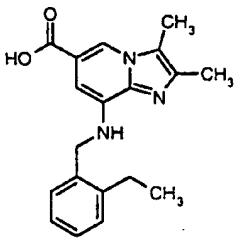
A2



A3

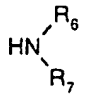


A4

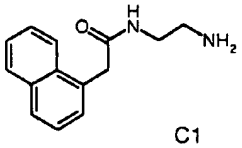


A5

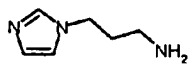
As the starting compound C in the reaction the following amines were used.



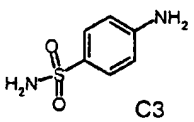
C =



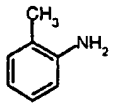
C1



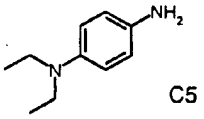
C2



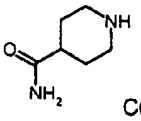
C3



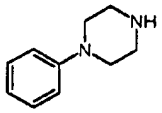
C4



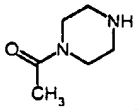
C5



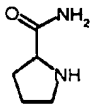
C6



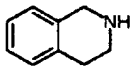
C7



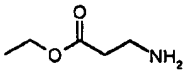
C8



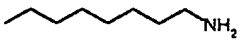
C9



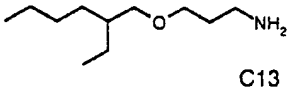
C10



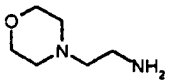
C11



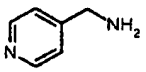
C12



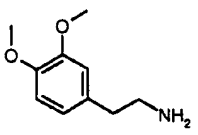
C13



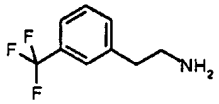
C14



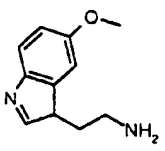
C15



C16



C17

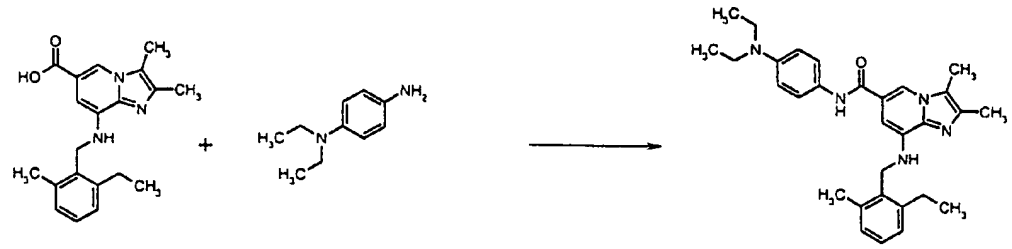


C18

The Examples 11-85 were prepered according to scheme 1

The primary or the secondary amino nitrogen is the nitrogen involved in the reaction.

e.g. A1 + C5 → Example 27



A1 C5 Example 27

$A_n + C_n \rightarrow$ Example 11-85

	A1	A2	A3	A4	A5
C1	Example 11	Example 12	Example 13	Example 14	Example 15
C2	Example 16	Example 17	Example 18	Example 19	Example 20
C3	-	-	-	-	Example 21
C4	Example 22	Example 23	Example 24	Example 25	Example 26
C5	Example 27	Example 28	Example 29	Example 30	Example 31
C6	Example 32	Example 33	Example 34	Example 35	Example 36
C8	Example 37	Example 38	Example 39	Example 40	Example 41
C9	Example 42	Example 43	Example 44	Example 45	Example 46
C10	Example 47	Example 48	Example 49	Example 50	Example 51
C11	-	Example 52	Example 53	Example 54	Example 55
C12	-	Example 56	Example 57	Example 58	Example 59
C13	-	Example 60	Example 61	Example 62	Example 63
C14	-	-	Example 64	Example 65	Example 66
C15	Example 67	Example 68	Example 69	Example 70	Example 71
C16	-	Example 72	Example 73	Example 74	Example 75
C17	Example 76	Example 77	Example 78	Example 79	Example 80
C18	Example 81	Example 82	Example 83	Example 84	Example 85

2. PREPARATION OF INTERMEDIATES

Example 2.1

Synthesis of 8-(2-ethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2-ethylbenzylamino)-2.3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (1.0 g. 0.0031 mol) and sodium hydroxide (1.2 g, 0.031 mol) were solved in ethanol (95 %)(30 ml) and

was refluxed overnight. The solvent was evaporated under reduced pressure and to the residue was added water. The pH was adjusted to 7 by addition of conc HCl (2.6 ml) and the solid that precipitated was isolated by filtration, washed with water and dried to give 1.0 g (99 %) of the title compound.

^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.2 (t, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.45 (d, 2H), 6.3 (s, 1H), 6.45 (t, 1H), 7.05-7.25 (m, 4H), 7.95 (s, 1H)

Example 2.2

Synthesis of 8-(2,6-diethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2,6-diethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (1.5 g, 0.0043 mol) and sodium hydroxide (1.7 g, 0.043 mol) were solved in ethanol (95 %) (30 ml).
The title compound were prepared according to Example 1.4. (Yield: 1.5 g, 99 %)

^{1}H-NMR (400 MHz,DMSO-d_6): δ 1.14 (t, 6H), 2.22 (s, 3H), 2.37 (s, 3H), 2.67 (q, 4H), 4.37 (d, 2H), 4.89 (t, 1H), 6.68 (s, 1H), 7.11 (d, 2H), 7.23 (t, 1H), 8.09 (s, 1H)

Example 2.3

Synthesis of 8-(2,6-dimethyl-4-fluorobenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2,6-dimethyl-4-fluorobenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.47 g, 0.0034 mol) and sodium hydroxide (1.7 g, 0.034 mol) were solved in ethanol (95 %) (30 ml).
The title compound were prepared according to Example 2.1. (Yield: 1.1 g, 95 %)

^{1}H-NMR (400 MHz,DMSO-d_6): δ 2.23 (s, 3H), 2.34 (s, 6H), 2.36 (s, 3H), 4.31 (d, 2H), 5.04 (bs, 1H), 6.70 (s, 1H), 6.90 (d, 2H), 8.02 (s, 1H)

Example 2.4

Synthesis of 8-(2-isopropyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2-isopropyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.2 g, 0.0027 mol) and sodium hydroxide (1.1 g, 0.027mol) were solved in ethanol(95 %) (25 ml).
The title compound were prepared according to Example 2.1. (Yield: 1.1 g, 95 %)

^{1}H-NMR (300 MHz.DMSO-d_6): δ 1.69 (d, 6H), 2.74 (s, 3H), 2.85 (s, 3H), 2.89 (s, 3H), 3.73 (m, 1H), 4.90 (d, 2H), 5.48 (t, 1H), 7.19 (s, 1H), 7.55-7.61 (m, 1H), 7.70-7.76 (m, 2H), 8.60 (s, 1H)

Example 2.5

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (11.0 g, 0.025 mol) and sodium hydroxide (7.0 g, 0.17 mol) were solved in ethanol(95 %) (120 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and to the residue was added water (150 ml). The pH was adjusted to 5 by addition of conc HCl and acetic acid and the solid that precipitated was isolated by filtration, washed with water and acetone, and dried to give 7.6 g (88 %) of the title compound

^{1}H-NMR (500 MHz.DMSO-d_6): δ 1.15 (t, 3H), 2.26 (s, 3H), 2.34 (s, 3H), 2.39 (s, 3H), 2.69 (q, 2H), 4.38 (d, 2H), 5.2 (bs, 1H), 6.73 (s, 1H), 7.07-7.2 (m, 3H), 8.12 (s, 1H)

Example 2.6

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide (0.02 g, 0.057 m mol) and sodium hydroxide (0.02 g, 0.29 mmol) were solved in ethanol (95 %) (1 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and to the residue was added water (1 ml). The pH was adjusted to 5 by addition of acetic acid and the solid that precipitated was isolated by filtration, washed with water and dried to give 0.012 g (60 %) of the title compound.

^{1}H-NMR (300 MHz.DMSO-d_6): δ 1.14 (t, 3H), 2.22 (s, 3H), 2.33 (s, 3H), 2.67 (q, 2H), 4.33 (d, 2H), 4.55 (bs, 1H), 4.67 (s, 2H), 6.83 (s, 1H), 7.06-7.24 (m, 3H), 8.15 (s, 1H)

BIOLOGICAL TESTS

1. In vitro experiments

Acid secretion inhibition in isolated rabbit gastric glands

Inhibiting effect on acid secretion *in vitro* in isolated rabbit gastric glands was measured as described by Berglindh et al. (1976) Acta Physiol. Scand. 97, 401-414.

Determination of H^+,K^+-ATPase activity

Membrane vesicles (2.5 to 5 µg) were incubated for 15 min at +37°C in 18 mM Pipes/Tris buffer pH 7.4 containing 2 mM $MgCl_2$, 10 mM KCl and 2 mM ATP. The ATPase activity

was estimated as release of inorganic phosphate from ATP, as described by LeBel et al. (1978) Anal. Biochem. 85, 86-89.

2. In vivo experiments

Inhibiting effect on acid secretion in female rats

Female rats of the Sprague-Dawly strain are used. They are equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of gastric secretions and administration of test substances, respectively. A recovery period of 14 days after surgery is allowed before testing commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula with tap water (+37°C), and 6 ml Ringer-Glucose given subcutaneously. Acid secretion is stimulated with infusion during 2.5-4 h (1.2 ml/h, subcutaneously) of pentagastrin and carbachol (20 and 110 nmol/kg·h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substances or vehicle are given either at 60 min after starting the stimulation (intravenous and intraduodenal dosing, 1 ml/kg), or 2 h before starting the stimulation (oral dosing, 5 ml/kg, gastric cannula closed). The time interval between dosing and stimulation may be increased in order to study the duration of action. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 M, and acid output calculated as the product of titrant volume and concentration.

Further calculations are based on group mean responses from 4-6 rats. In the case of administration during stimulation; the acid output during the periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. In the case of administration before stimulation; percentage inhibition is calculated directly from acid output recorded after test compound and vehicle.

Bioavailability in rat

Adult rats of the Sprague-Dawley strain are used. One to three days prior to the experiments all rats are prepared by cannulation of the left carotid artery under anaesthesia. The rats used for intravenous experiments are also cannulated in the jugular vein (Popovic (1960) J. Appl. Physiol. 15, 727-728). The cannulas are exteriorized at the nape of the neck.

Blood samples (0.1 - 0.4 g) are drawn repeatedly from the carotid artery at intervals up to 5.5 hours after given dose. The samples are frozen until analysis of the test compound.

Bioavailability is assessed by calculating the quotient between the area under blood/plasma concentration (AUC) curve following (i) intraduodenal (i.d.) or oral (p.o.) administration and (ii) intravenous (i.v.) administration from the rat or the dog, respectively.

The area under the blood concentration vs. time curve, AUC, is determined by the log/linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) following intraduodenal or oral administration is calculated as F(%) = (AUC (p.o. or i.d.) / AUC (i.v.)) x 100.

Inhibition of gastric acid secretion and bioavailability in the conscious dog.

Labrador retriever or Harrier dogs of either sex are used. They are equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhaim-pouch for the collection of gastric secretion.

Before secretory tests the animals are fasted for about 18 h but water is freely allowed. Gastric acid secretion is stimulated for up to 6.5 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and

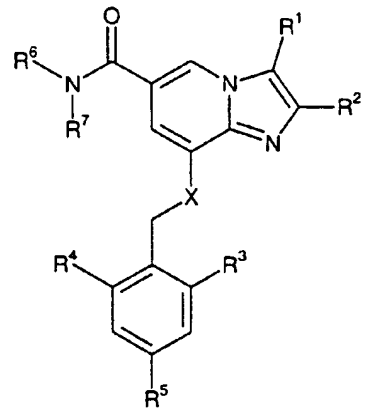
gastric juice collected in consecutive 30-min fractions. Test substance or vehicle is given orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenham-pouch dog.

The acidity of the gastric juice samples are determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition is calculated from fractional responses elicited by test compound and vehicle.

Blood samples for the analysis of test compound concentration in plasma are taken at intervals up to 4 h after dosing. Plasma is separated and frozen within 30 min after collection and later analyzed. The systemic bioavailability (F%) after oral or i.d. administration is calculated as described above in the rat model.

CLAIMS

1. A compound of the formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

(a) H,

(b) CH_3, or

(c) CH_2OH;

R^2 is

(a) CH_3, or

(b) CH_2CH_3;

R^3 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^4 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^5 is

(a) H, or

(b) halogen;

R^6 and R^7 are independently selected substituents, comprising C, H, N, O, S , Se , P or Halogen atoms, which give compounds of Formula I a molecular weight ≤ 600, provided that at least one of R^6 and R^7 can not be H, C_1–C_6 alkyl, hydroxylated C_1–C_6 alkyl,or C_1–C_6 alkoxy-substituted C_1–C_6 alkyl, and

X is

(a) NH, or

(b) O.

2. A compound according to formula I wherein R^1 is CH_3 or CH_2OH; R^2 is CH_3 or CH_2CH_3; R^3 is CH_3 or CH_2CH_3; R^4 is CH_3 or CH_2CH_3; R^5 is H, Br, Cl, or F; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl or C_1-C_6 alkoxy-substituted C_1-C_6 alkyl)

:

(a) H,

(b) C_1–C_6 alkyl,

(c) hydroxylated C_1–C_6 alkyl,

(d) C_1–C_6 alkoxy-substituted C_1–C_6 alkyl,

(e) C_2–C_6 alkenyl,

(f) C_2–C_6 alkynyl,

(g) halogenated C_1–C_6 alkyl,

(h) C_3–C_8 cycloalkyl,

(i) cycloalkyl-substituted C_1–C_6 alkyl,

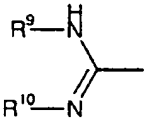
(j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, or CN or NH_2SO_2,

(k) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl , optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN or NH_2SO_2,

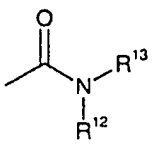
(l) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, NH_2SO_2–, C_1–C_6 alkyl–SO_2NH–, $ArSO_2NH$–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–SO_2–, C_1–C_6 alkyl–C=O–, NH_2–, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$N–, ArCONH–, Ar(C_1-C_6 alkyl)CONH, $ArNHSO_2$–, (Ar)$_2$–N–SO_2–, C_1–C_6 alkyl–$NHSO_2$–, ArS–, ArSO–, $ArSO_2$–, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl)$_2$–NCONH–, ArNHCONH–, (C_1–C_6 alkyl)$_2$–N–SO_2– , Ar–O– , Ar–NH– , Ar(C_1–C_6 alkyl)N– , hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN, nitro, amino, C_1–C_6 alkyl–NH–, or (C_1–C_6 alkyl)$_2$N–,

(m) C_7-C_{12} ,

(n) OH, O-C_1–C_6 alkyl, or O-hydroxylated C_1–C_6 alkyl,

(o)  wherein R^9 and R^{10} are independently H or C_1-C_6 alkyl,

(p) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, C_1-C_6 alkyl-OOC- or an amino carbonyl group with the formula



wherein R^{12}, R^{13} are the same or different H, or C_1-C_6 alkyl

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline), or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2 I wherein R^1 is CH_3 or CH_2OH; R^2 is CH_3, R^3 is CH_3 or CH_2CH_3; R^4 is CH_3 or CH_2CH_3; R^5 is H, Br, Cl, or F; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl or C_1-C_6 alkoxy-substituted C_1-C_6 alkyl),

(a) H,

(b) C_1–C_6 alkyl,

(c) hydroxylated C_1–C_6 alkyl,

(d) C_1–C_6 alkoxy-substituted C_1–C_6 alkyl,

(e) halogenated C_1–C_6 alkyl,

(f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, or CN;

(g) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, or OH,

(h) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–C=O–,-ArCONH–, Ar(C_1-C_6 alkyl)CONH, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl)$_2$–NCONH–, ArNHCONH–,hydroxylated C1-C6

alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN,

(i) C_7-C_{12} alkyl.

(j) OH ,

(k) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, or C_1-C_6 alkyl -OOC,

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline)

4. The compound according to claims 1 to 3 being;

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine,

N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

N-[2-(dimethylamine)-2-oxoethyl]-8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide,

(8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone,

1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin -6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide,

8-(2-ethyl-6-methylbenzylamino)-N-hydroxy-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

(2-ethyl-6 methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

(8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-

hydroxy-1-pyrrolidinyl)methanone,

N-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

8-(2-ethyl-6-methylbenzylamino-3-(hydroxymethyl)-2-methyl-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine,

N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine,

4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid,

or a pharmaceutically acceptable salt thereof.

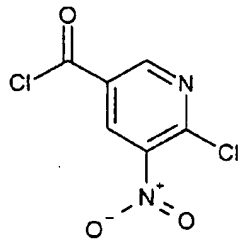
5. A compound according to any of claims 1-4 as a hydrochloride or mesylate salt.

6. Products containing a compound according to any of claims 1-5 and at least one antimicrobial agent as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.

7. Products containing a compound according to any of claims 1-5 and at least one proton pump inhibitor as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.

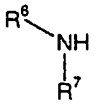
8. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH, comprising

(a) reacting a compound of the Formula II



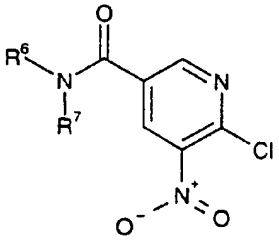
II

with a compound of the Formula III



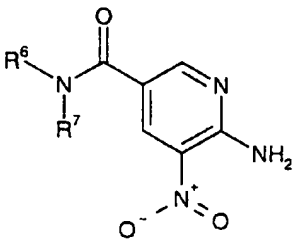
III

wherein R^6 and R^7 are as defined in claim 1, in an inert solvent, to a compound of the Formula IV,



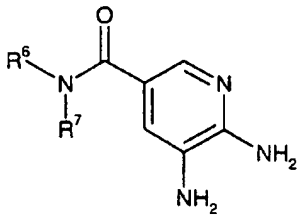
IV

(b) reacting a compound of the Formula IV wherein R^6 and R^7 are as defined in claim 1, with ammonia in an inert solvent to a compound of the Formula V



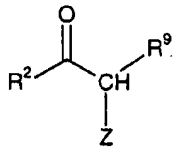
V

(c) reducing a compound of the Formula V wherein R^6 and R^7 are as defined in claim 1 in an inert solvent under standard conditions to a compound of the Formula VI



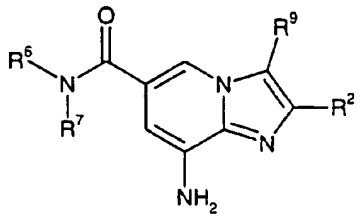
VI

(d) reacting a compound of the Formula VI wherein R^6 and R^7 are as defined in claim 1 with a compound of Formula VII



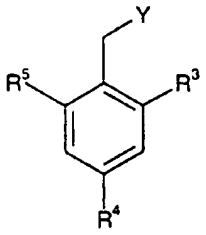
VII

wherein R^2 is as defined in claim 1, Z is a leaving group and R^9 represent H, CH_3 or an ester group, in an inert solvent with or without a base to a compound of the Formula VIII



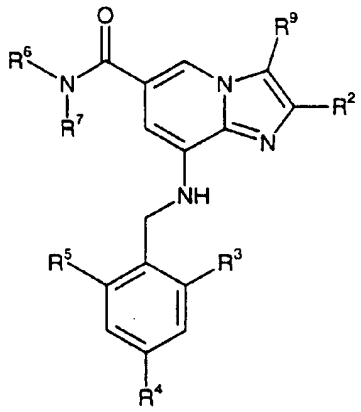
VIII

(e) reacting a compound of the Formula VIII wherein R^6, R^7 and R^2 are as defined in claim 1, and R^9 is H, CH_3 or an ester group with a compound of Formula IX



IX

wherein R^3, R^4, and R^5 are as defined in claim 1, and Y is a leaving group in an inert solvent with or without a base, to a compound of the Formula X

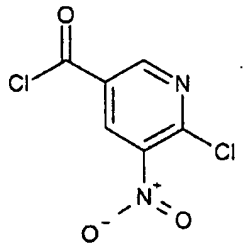


X

(f) reducing a compound of Formula X wherein R^9 is an ester group in an inert solvent to a compound of the Formula I wherein R^1 is CH_2OH and X is NH.

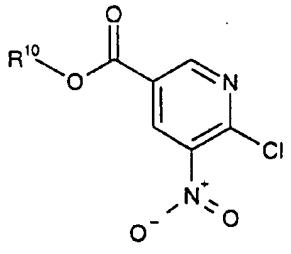
9. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH and R^1 is H or CH_3, comprising

(a) reacting a compound of the Formula II



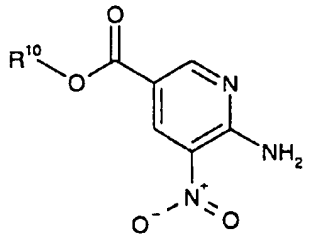
II

with an alcohol compound of the general formula R^{10}-OH, wherein R^{10} is an alkyl group under standard conditions, to a compound of the Formula XI



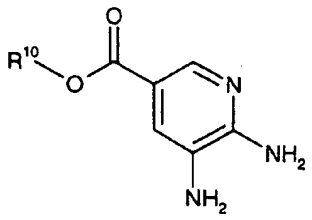
XI

(b) reacting a compound of the Formula XI wherein R^{10} is an alkyl group, with ammonia in an inert solvent under standard conditions to a compound of the Formula XII



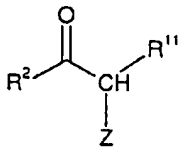
XII

(c) reducing a compound of the Formula XII wherein R^{10} is an alkyl group in an inert solvent under standard conditions to a compound of the Formula XIII



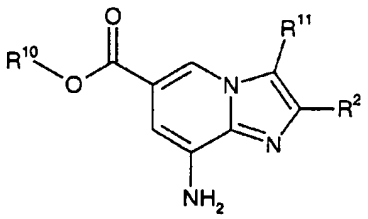
XIII

(d) reacting a compound of the Formula XIII wherein R^{10} is an alkyl group with a compound of Formula XIV



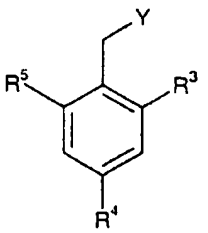
XIV

wherein R^2 is as defined in claim 1, Z is a leaving group and R^{11} represent H or CH_3, in an inert solvent with or without a base to a compound of the Formula XV



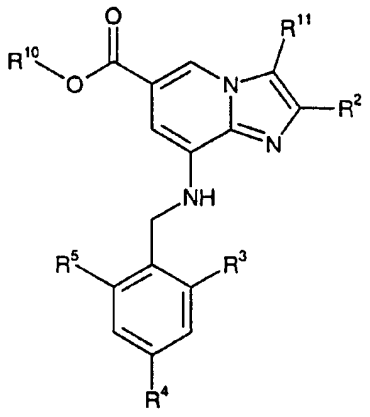
XV

(e) reacting a compound of the Formula XV wherein R^{10} is an alkyl group, R^2 are as defined in claim 1 and R^{11} is H or CH3 with a compound of Formula IX



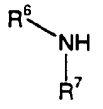
IX

wherein R^3, R^4, and R^5 are as defined in claim 1 and Y is a leaving group in an inert solvent with or without a base to a compound of the Formula XVI



XVI

(f) reacting a compound of Formula XVI wherein R^2, R^3, R^4 and R^5 are as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3 with a compound of Formula III

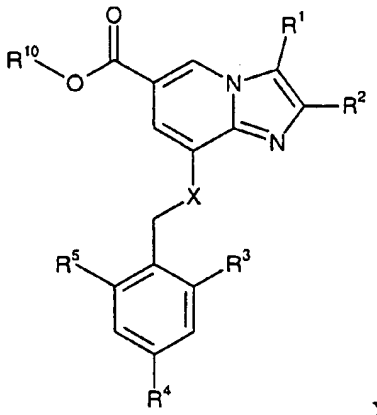


III

wherein R^6 and R^7 are as defined in claim 1, under standard conditions, to a compound of Formula I wherein R^1 is H or CH_3 and X is NH.

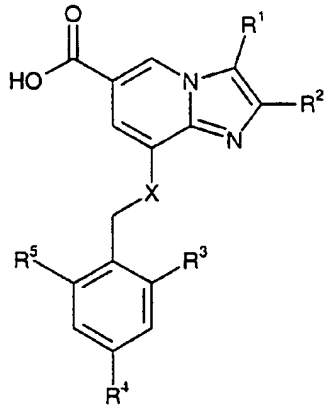
10. A process for the preparation of a compound according to any one of claims 1 to 5 comprising

(a) treating a compound of Formula XVII



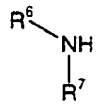
XVII

wherein R^1, R^2, R^3, R^4, R^5 and X are as defined in claim 1 and R^{10} is an alkyl group, with acid or base under standard conditions to a compound of Formula XVIII



XVIII

(b) reacting a compound of Formula XVIII wherein R^1, R^2, R^3, R^4, R^5 and X is defined in claim 1 with a compound of Formula III



III

wherein R^6 and R^7 are as defined in claim 1, in the presence of a coupling reagent in an inert solvent under standard conditions, to a compound of Formula I.

11. A compound according to any one of claims 1 to 5 for use in therapy.

12. A pharmaceutical formulation containing a compound according to any one of claims 1 to 5 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.

13. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the inhibition of gastric acid secretion.

14. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases.

15. Use of a compound according to any one of claims 1 to 5 the manufacture of a medicament for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the said salt is adapted to be administered in combination with at least one antimicrobial agent.

16. A method for inhibiting gastric acid secretion which comprises administering to a mammal, including man, in need of such inhibition an effective amount of a compound according to any one of claims 1 to 5.

17. A method for the treatment of gastrointestinal inflammatory diseases which comprises administering to a mammal, including man, in need of such treatment an effective amount of a compound according to any one of claims 1 to 5.

18. A method for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a

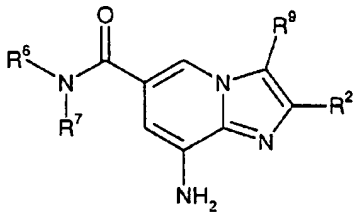
compound as claimed in any one of claims 1 to 5, wherein the said salt is administered in combination with at least one antimicrobial agent.

19. A pharmaceutical formulation for use in the inhibition of gastric acid secretion wherein the active ingredient is a compound according to any one of claims 1 to 5.

20. A pharmaceutical formulation for use in the treatment of gastrointestinal inflammatory diseases wherein the active ingredient is a compound according to any one of claims 1 to 5.

21. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the active ingredient is a compound according to any one of claims 1 to 5 in combination for simultaneous, separate or sequential use or together with at least one antimicrobial agent.

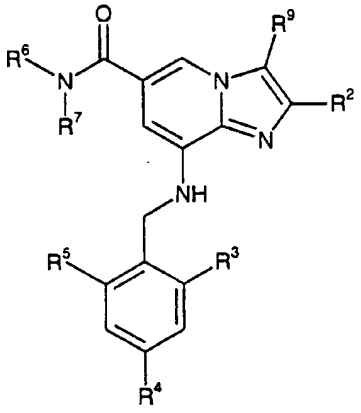
22. A compound of the formula VIII



VIII

wherein R^2, R^6 and R^7 are as defined in claim 1, and R^9 is H, CH_3 or an ester group.

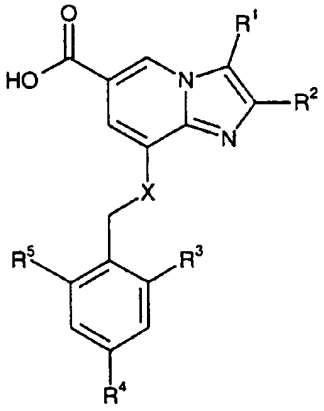
23. A compound of the formula X



X

wherein R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim 1, and R^9 is an ester group.

24. A compound of the formula



XVIII

wherein R^1, R^2, R^3, R^4 R^5 and X are as defined in claim 1.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

Astra Aktiebolag
Intellectual Property, Patents
151 85 Södertälje

PCT

NOTIFICATION OF DECISION CONCERNING REQUEST FOR RECTIFICATION

(PCT Rule 91.1(f))

Applicant's or agent's file reference H 2123-1 WO	Date of mailing *(day/month/year)* 18-06-1999
International application No. PCT/SE99/00662	REPLY DUE NONE However, see last paragraph below
Applicant Astra Aktiebolag et al	International filing date *(day/month/year)* 23-04-1999

The applicant is hereby notified that this International Searching Authority has considered the request for rectification of obvious errors in the international application/in other papers submitted by the applicant to this Authority, and that it has decided:

1. ☐ to authorize the rectification:
   - ☐ as requested by the applicant.
   - ☐ to the extent set forth below*:

2. ☒ to refuse to authorize the rectification or part of it for the following reasons*:

The rectification itself is not obvious in the sense that *anyone would immediately* realize that nothing else could have been intended.

A copy of this notification, together with a copy of the applicant's request for rectification, has been sent to the receiving Office and to the International Bureau.

* **If the authorization of the rectification has been refused in whole or in part,** the applicant may request the International Bureau, before the technical preparations for international publication have been completed and subject to the payment of a fee, to publish the request for rectification together with the international application. See Rule 91.1(f), third and fourth sentences, and, for the amount of the fee, see the *PCT Applicant's Guide*, Volume I/A, Annex B2(IB).

Name and mailing address of the ISA/ Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Telex 17978 PATOREG-S	Authorized officer Jenny Anderberg Telephone No. 08-782 25 00 Jenny Anderberg

Form PCT/ISA/217 (July 1998)

ASTRA

Patent- och Registreringsverket
Box 5055
102 42 STOCKHOLM

Första Posten

June 8, 1999

Our ref.
H 2123-1 WO

Your ref.
PCT/SE99/00662

Re: Request to correct obvious errors according to PCT-rule 91.

Dear Sirs,

We hereby kindly request rectification of the specification of the above identified international patent application in accordance with PCT-rule 91.1(d). The request refers to correction of obvious typing errors.

Please find enclosed substitute sheets, page 11, 14, 19-20, 49, 51-53, and 56, wherein the substituents denoted R^4 and R^5 have been replaced, whereby each and every formula have regained its original substitution pattern found e.g. in the general Formula I on page 2 and in all other related formulas.

We earnestly request that the substitute sheets are included in the present application before publishing.

Yours sincerely,

Christer Hällgren, Ph.D.
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16.02.2000 FPA-gg

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00662

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 471/04, A61K 31/435
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0308917 A2 (FUJISAWA PHARMACEUTICAL, CO., LTD.), 29 March 1989 (29.03.89) --	1-15,19-23
A	J. Med. Chem., Volume 28, 1985, James J. Kaminski et al, "Antiulcer Agents. 1. Gastric Antisecretory and Cytoprotective Properties of Substituted Imidazo(1,2-a)pyridines" page 876 - page 892 --	1-15,19-23
A	EP 0033094 A1 (SCHERING CORPORATION), 5 August 1981 (05.08.81) --	1-15,19-23
A	EP 0228006 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 8 July 1987 (08.07.87) --	1-15,19-23

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 Sept 1999	09 -09- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00662

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0204285 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 10 December 1986 (10.12.86) --	1-15,19-23

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00662

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-18
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-15, 19-23

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00662

The subjects, defined by the problems and their means of solution, as listed below are so different from each other that no technical relationship or interaction can be appreciated to be present so as to form a single general inventive concept. The acceptance of a single general inventive concept covering the end products as well as products used to prepare these and products (intermediates) implies that when several claimed intermediates are implied in different reactions, these intermediates are technically closely inter-connected with the end products as well as with themselves by their use for incorporation of the same essential structural part into the end products.

1. claims 1-15, 19-21, and claims 22 and 23, intermediates VIII and X

2. claim 24, intermediate XVIII

The special technical feature of invention 1 is compound I containing an amide group in position 6 and intermediates VIII and X, which are specially designed for the preparation of compound I. Compounds I, VIII and X do not contain a common technical feature together with intermediate XVIII. Therefore, a single inventive concept based on the relationship intermediates/end products is lacking.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.
PCT/SE 99/00662

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0308917 A2	29/03/89	AU 2278388 A	06/04/89
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